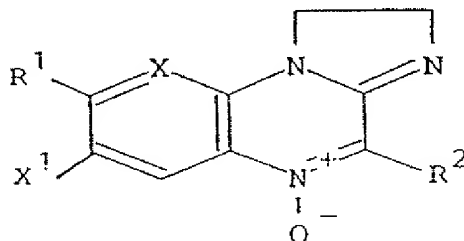




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB93/01950 <b>(22) International Filing Date:</b> 15 September 1993 (15.09.93)  <b>(30) Priority data:</b> 9219566.8 16 September 1992 (16.09.92) GB  <b>(71) Applicant:</b> BRITISH TECHNOLOGY GROUP LIMITED [GB/GB]; 101 Newington Causeway, London SE1 6BU (GB).  <b>(72) Inventors:</b> ADAMS, Gerald, Edward ; FIELDEN, Edward, Martin ; NAYLOR, Matthew, Alexander ; STRATFORD, Ian, James ; MRC Radiobiology Unit, Chilton, Didcot, Oxon OX11 0RD (GB).		<b>(74) Agents:</b> WOODS, Geoffrey, Corlet et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).  <b>(81) Designated States:</b> AU, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** NOVEL BIOREDUCTIVE AGENTS

(I)

**(57) Abstract**

Quinoxaline or pyrido pyrazine derivatives of formula (I) wherein  $R^1$  is: hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino, aminoalkyl(N-alkyl)amino or aminoalkoxy unsubstituted or substituted on the terminal amino group by one or two alkyl groups or a divalent group which forms a saturated heterocyclic ring together with the nitrogen atom to which it is attached, hydroxyalkylamino or haloalkylamino or an N-alkyl derivative thereof, or hydroxyalkoxy or haloalkoxy; a heterocyclic group which is a 1-pyrrolidino, 1-piperidino, 1-morpholino group, unsubstituted or substituted; or a 1-piperazino group which is unsubstituted or substituted substituents in the 2- or 3-position and in the 4-position is unsubstituted or N-substituted by haloalkyl, cycloalkyl, pyridyl or phenyl;  $R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted; X is  $-CH=$  or  $-N=$ ; and  $X^1$  is hydrogen or halogen; and pharmaceutically acceptable salts thereof are useful in the treatment of tumours, and in particular hypoxic tumours. Processes for producing the compounds and pharmaceutical compositions comprising them.

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NOVEL BIOREDUCTIVE AGENTS

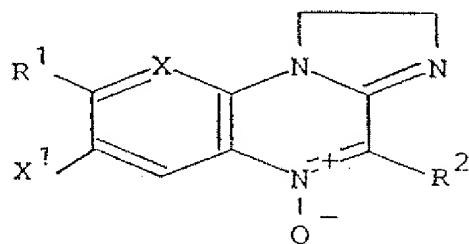
The present invention relates to dihydroimidazo-  
quinoxaline and dihydroimidazo-pyridopyrazines useful in  
the treatment of cancer. It further relates to processes  
5 for their preparation and pharmaceutical compositions  
containing them.

EP-A-214,632 discloses quinoxaline and pyridopyrazine  
derivatives which are useful as anti-anaerobic agents, for  
the treatment of diseases related to anaerobic bacteria.  
10 Such diseases include for example, post-operative sepsis  
following lower gastrointestinal surgery or female  
urinogenital surgery, pelvic inflammatory disease, ulcers,  
gangrene, trichomonal vaginitis, non-specific vaginitis,  
amoebiasis, giardiasis, periodontal disease, acne, and the  
15 like.

WO-A-93/00900 which was published after both the  
priority dates of the present case, discloses that the  
compounds disclosed in EP-A-214,632 and pharmaceutically  
acceptable salts thereof are useful in the treatment of  
20 tumours and particularly hypoxic tumours.

The present invention provides a quinoxaline or  
pyridopyrazine derivative of formula (I)

25



(I)

- 2 -

wherein R' is:

- hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a
- 5 divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino
- 10 unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being
- 15 substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkoxy unsubstituted or substituted on the amino group by one or two alkyl groups or by a divalent which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally
- 20 containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-alkyl)amino, or haloalkyloxy;
- 25 a heterocyclic group which is a 1-pyrrolidino, 1-piperidino or 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents, or an aziridino group unsubstituted or substituted by one or more or alkyl substituents; or

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a 1-piperazino-group which is unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents in the 2- or 3- position and in the 4-position is unsubstituted or N-substituted by haloalkyl, cycloalkyl of 5 to 7 carbon atoms (unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents), or pyridyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents) or phenyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents);

$R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen, haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy;

X is  $-CH=$  or  $-N=$ ; and

$X^1$  is hydrogen or halogen;

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms and the said haloalkyl groups contain one or more halogen atoms;

or a pharmaceutically acceptable salt thereof;

with the exclusion of (a) the compounds of formula (I) where  $R^1$  is hydrogen, X is  $-N=$ ,  $X^1$  is hydrogen and  $R^2$  is unsubstituted phenyl or 3-pyridyl, and  $R^1$  is hydrogen, X is  $-CH=$ ,  $X^1$  is hydrogen and  $R^2$  is 4-fluorophenyl, 3,4-dimethoxyphenyl, 3,4-ethylenedioxy or 3,4,5-trimethoxyphenyl and (b) the compound of formula (I) which is 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo [1,2a]

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quinoxaline 5-oxide.

According to further features the present invention provides processes for producing the compounds of the present invention and pharmaceutical compositions comprising compounds of formula (I) (including exclusions (a) and (b) from the compounds of the invention).

In the compounds of formula (I), the alkyl, haloalkyl and alkoxy groups may be either straight or branched.

It is preferred that any alkyl groups in the compounds of formula (I) (including alkyl groups which form part of alkoxy groups) be alkyl groups of 1 to 4 carbon atoms, i.e. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. Particularly preferred alkyl substituents are methyl, and ethyl, most preferably methyl.

In the compounds of formula (I) halogen atoms present as halogen substituents or in haloalkyl substituents may for example be fluorine, chlorine or bromine atoms.

In a first embodiment the group  $R^1$  is hydrogen or an alkyl group. Preferably  $R^1$  is other than hydrogen.

In a second embodiment the group  $R^1$  is an alkylamino, dialkylamino or alkoxy group, for example an alkylamino or dialkylamino group.

In a third embodiment the group  $R^1$  is an aminoalkylamino, aminoalkyl(N-alkyl)amino or aminoalkoxy group, substituted or unsubstituted on the terminal amino group, a hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino or hydroxyalkoxy group or a haloalkylamino, haloalkyl(N-

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alkyl)amino or haloalkoxy group.

R<sup>1</sup> may for example be aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups, amino(N-alkyl)amino unsubstituted  
5 or substituted on the terminal amino group by one or two alkyl groups, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, haloalkylamino, or haloalkyl(N-alkyl)amino.

Preferably when R<sup>1</sup> is an aminoalkylamino, aminoalkyl(N-alkyl)amino or aminoalkoxy group or a  
10 substituted derivative thereof, it is a group of formula (II):-



wherein Y is -O- or -NR<sup>5</sup>-, preferably -NR<sup>5</sup>-, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same or different and each is hydrogen or alkyl of  
15 1 to 6 carbon atoms, preferably hydrogen or methyl, and a is 2 or 3, preferably 2. Alternatively R<sup>3</sup> and R<sup>4</sup> may, together with the nitrogen atom to which they are attached form a heterocyclic ring, preferably containing 5 to 7 atoms, such as a pyrrolidino or piperidino ring, or which  
20 may contain an extra nitrogen or oxygen atom, such as a piperazino or morpholino ring. Such a ring may be unsubstituted or substituted by one or more alkyl, hydroxyl or halogen substituents and/or in the case of a heterocyclic ring containing an additional nitrogen atom  
25 unsubstituted at the nitrogen atom or N-substituted by alkyl, haloalkyl, cycloalkyl of 5 to 7 carbon atoms, pyridyl or phenyl. Such N-substituents may themselves be

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unsubstituted or substituted as hereinbefore defined in relation N-substituted piperazino groups R<sup>1</sup>.

Preferably when R<sup>1</sup> is a haloalkylamino, haloalkyl(N-alkyl)amino or haloalkoxy or hydroxyalkylamino

5 hydroxyalkyl(N-alkyl)amino group, or hydroxyalkoxy it is a group of formula (III):-



wherein Y<sup>1</sup> is -O- or -NR<sup>6</sup>-, preferably -NR<sup>6</sup>-, R<sup>6</sup> is hydrogen or alkyl of 1 to 6 carbon atoms, preferably hydrogen or  
10 methyl, Y<sup>2</sup> is halogen or hydroxyl, preferably hydroxyl and b is 2 or 3, preferably 2. R<sup>1</sup> may for example be haloalkylamino or haloalkyl(N-alkyl)amino or hydroxyalkylamino or hydroxyalkyl(N-alkyl)amino group.

In a fourth embodiment R<sup>1</sup> is an unsubstituted or  
15 substituted, preferably unsubstituted, 1-pyrrolidino, 1-piperidino, 1-morpholino or aziridino group.  
1- Morpholino groups are most preferred. When such a group is substituted it is preferably substituted by a single substituent. Preferred substituents include hydroxyl and  
20 alkyl, preferably methyl or ethyl, more preferably methyl, for pyrrolidino, piperadino and morpholino groups and methyl and ethyl, more preferably methyl, for aziridino groups.

In a fifth embodiment R<sup>1</sup> is an unsubstituted or  
25 substituted 1-piperazino group. Preferably the group is unsubstituted in the 2- and 3-positions. Where there is such substitution, there is preferably a single



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substituent, and preferred substituents include hydroxyl and alkyl, preferably methyl or ethyl, more preferably methyl.

Preferably the 1-piperazino is N-substituted in the  
5 4-position by a haloalkyl, cycloalkyl, pyridyl or phenyl group.

Preferred haloalkyl substituents are fluoroalkyl substituents preferably containing more than one fluorine atom, for example 2,2,2-trifluoroethyl or trifluoromethyl,  
10 preferably 2,2,2-trifluoroethyl.

Preferred cycloalkyl substituents are cyclohexyl substituents. Preferably such a cycloalkyl substituent is itself unsubstituted. When such a cycloalkyl group is substituted it is preferably substituted by a single  
15 substituent and preferred substituents include hydroxyl and alkyl, preferably methyl or ethyl, more preferably methyl.

Of pyridyl or phenyl substituents, pyridyl substituents are preferred and may be 2- or 3-, preferably 2-pyridyl. Such phenyl and pyridyl groups are preferably  
20 themselves unsubstituted. When such a group is itself substituted preferred substituents are as defined in relation to R<sup>2</sup> below.

In the compounds of formula (I) R<sup>2</sup> may be unsubstituted or substituted, preferably unsubstituted.  
25 Hydrocarbyl aromatic groups may for example be phenyl or

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naphthyl, preferably phenyl, and heterocyclyl aromatic groups may for example be pyridyl or thiophenyl, preferably pyridyl. Most preferably  $R^2$  is unsubstituted or substituted phenyl. Pyridyl groups may be 2- or  
5 3-, preferably 3-, pyridyl. Naphthyl groups may be 1- or 2-, preferably 2-, naphthyl. Thiophenyl groups may be 2- or 3- thiophenyl.

Where the group  $R^2$  is substituted it is preferably substituted by 1 or 2 substituents, chosen from halogen,  
10 haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy. Preferred substituents include halogen, for example fluorine, chlorine or bromine, haloalkyl, for example trifluoromethyl, nitro, and alkoxy, for example methoxy and ethoxy, preferably methoxy. Where  $R^2$  is substituted  
15 phenyl, preferably it is 4-substituted phenyl, more preferably 4-halophenyl and most preferably 4-fluorophenyl.

In the compounds of formula (I) X is preferably  $-N=$ .

Preferably  $X^1$  is hydrogen.

Salts of the compounds of formula (I) may be any  
20 pharmaceutically acceptable acid addition salts of the compounds of formula (I). Examples of suitable salts include, salts of inorganic acids such as chlorides, bromides, iodides, phosphates and sulphates and salts of organic acids such as acetates, citrates, lactates and  
25 tartrates. Salts of inorganic acids are preferred, hydrochlorides, hydrobromides and hydroiodides are more preferred. Hydrochlorides are most preferred.

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Particular examples of the compounds of formula (I)  
are:-

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-  
5 a]quinoxaline 5-oxide,

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]  
pyrido [3,2-e] pyrazine 5-oxide,

10 1,2-Dihydro-4-(4-fluorophenyl)imidazo[1,2-a] pyrido [3,2-e]  
pyrazine 5-oxide,

1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-  
phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,  
15

1,2-Dihydro-8-(1-methyl-1-hydroxyethylamino)-4-  
phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(1-aminopropyl)amino-4-phenylimidazo [1,2-a]  
20 pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a]  
pyrido [3,2-e] pyrazine 5-oxide,

25 1,2-Dihydro-8-(4-cyclohexylpiperazin-1-yl)-4-phenylimidazo  
[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

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1,2-Dihydro-8-(2-methylaziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a]  
5 pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

10 1,2-Dihydro-8-(4-(2-pyridyl)piperazin-1-yl)-4-phenylimidazo  
[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a]  
quinoxaline 5-oxide,  
15

1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a]  
quinoxaline 5-oxide,

1,2-Dihydro-8-(pyrrolidin-1-yl)-4-phenylimidazo [1,2-a]  
20 quinoxaline 5-oxide,

1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

25 1,2-Dihydro-4-(3-pyridyl)-imidazo [1,2-a] pyrido [3,2-e]  
pyrazine 5-oxide,

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1,2-Dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine  
5-oxide,

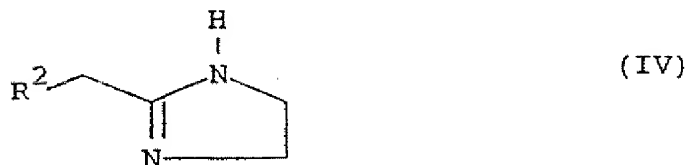
1,2-Dihydro-8-(aziridin-1-yl)-4-phenylimidazo [1,2-a]  
5 pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-methoxy-4-phenylimidazo [1,2-a] pyrido [3,2-  
e] pyrazine 5-oxide, and

10 1,2-Dihydro-8-(1-(dimethylamino)ethoxy)-4-phenylimidazo  
[1,2-a] pyrido [3,2-e] pyrazine 5-oxide.

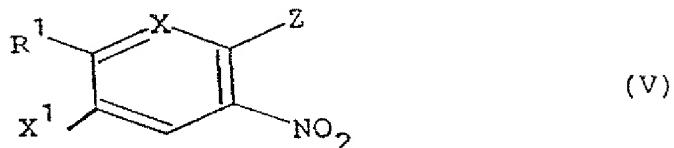
These compounds may be in the form of a free base or  
of salts, and in particular hydrochloride salts.

15 The compounds of formula (I) may be produced, by  
reacting a compound of formula (IV):



20

in which R² is as hereinbefore defined, with a  
compound of formula (V)



25

in which Z is halogen and R¹, X and X¹ are as hereinbefore  
defined.

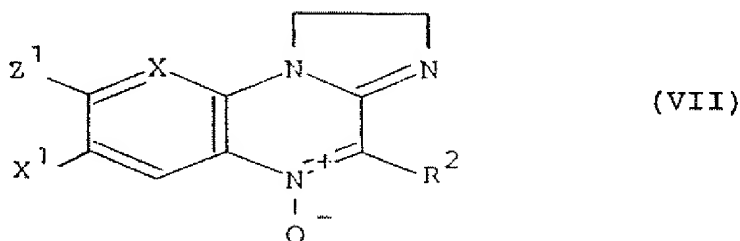
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The reaction is generally carried out under basic conditions in an organic solvent as reaction medium, such as acetonitrile or an alcohol, for example 2-propanol. Generally the reaction is carried out at from 50 to 110°C, preferably about 80°C.

Compounds of formula (I) where R<sup>1</sup> is other than hydrogen or alkyl, alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy, may alternatively be produced by reacting a compound of formula (VI):-



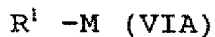
wherein R<sup>1</sup> is as hereinbefore defined with a compound of formula (VII)



wherein R<sup>2</sup>, X and X<sup>1</sup> are as hereinbefore defined and Z<sup>1</sup> is halogen.

Generally reaction with a compound (VI) is carried out in an organic solvent, such as an alcohol, for example propan-2-ol at a temperature from 60 to 110°C.

Compounds of formula (I) where R<sup>1</sup> is alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy may be produced by reacting a metal alkoxide, (VIA)



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in which R<sup>1</sup> is alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy, and M is a metal, for example an alkali metal, with a compound of formula (VII) as hereinbefore defined.

5           Generally reaction with an alkoxide (VIA) is performed in an alcoholic solution of alkoxide, for example in the corresponding alcohol as solvent or in methanol or ethanol, at a temperature from 50 to 80°C.

10           The compound of formula (I) thus obtained may be purified by chromatography, for example on silica gel, or recrystallised using an appropriate solvent.

15           Compounds of formula (I) may be converted into pharmaceutically acceptable salts in conventional manner for the formation of acid addition salts. For example, the salts of the present invention may be produced by reaction with an organic acid, or more preferably an inorganic acid such as hydrochloric acid, in an organic reaction medium.

20           The compounds of formulae (IV), (V), (VI), (VIA) and (VII) are compounds which may be prepared using known methods. In particular compounds of formula (IV) may be obtained by reacting an acetonitrile derivative R<sup>2</sup>CH<sub>2</sub>CN in ethylenediamine at elevated temperature, e.g. about 200°C for 24 to 48 hours. Compounds of formula (VII) may be obtained according to procedures described in EP-A-214,632.

25           The compounds of formula (I) and salts thereof are useful in increasing the sensitivity of tumour cells to

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radiation in radiotherapy and as bio-reductive agents. A compound is administered to a patient having a radiation-treatable cancer, prior to or after, more typically shortly after irradiation of the tumour, in an amount effective to  
5 increase the sensitivity of the tumour cells to the effects of the irradiation.

Any solid tumour, which may have regions where cells are radiobiologically hypoxic and become resistant to ionising radiation, may be treated. Examples of such  
10 tumours are epithelial tumours of the head, neck, thorax and abdomen, soft tissue sarcomas and brain tumours. The compounds of formula (I) and salts thereof can therefore be employed in the radiotherapy of all such solid tumours where hypoxic cells are known or suspected to exist.

15 The compounds of formula (I) and salts thereof may also be used where an agent having differential hypoxic cytotoxicity is required. The compounds can be employed for chemopotentialisation of a chemotherapeutic agent or as a chemotherapeutic by administration of a compound to a  
20 patient having a localised or metastatic cancer. Administration is carried out prior to, simultaneously with or after administration of, typically prior to or simultaneously with, a chemotherapeutic agent such as melphalan, cyclophosphamide, 5-fluorouracil, adriamycin,  
25 CCNU(1<sup>-</sup>-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) or tumour necrosis factor (TNF). Any solid tumours, such as above, which are primary or secondary deposits, where it is



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known or suspected that hypoxic cells are present can therefore benefit from treatment employing a compound of formula (I) or a salt thereof.

The compounds of formula (I) and salts thereof are  
5 useful in particular for the treatment of hypoxic tumours. However they may also be useful in the treatment of other tumours rich in enzymes required to activate them as bioreductive agents or radiosensitisers. Such enzymes may include cytochrome P450, NADPH dependent cytochrome P450  
10 reductase, DT-diaphorase and xanthine oxidase.

The compounds of formula (I) and salts thereof may be administered orally or parenterally. The amount administered depends on factors such as the cancer, the condition of the patient and the body weight of the  
15 patient. Typically, however, doses of 50 to 1000mg/m<sup>2</sup> of a patient's body area may be employed.

Accordingly, the present invention further provides a pharmaceutical composition comprising a compound of formula (I), as hereinbefore defined or a pharmaceutically  
20 acceptable salt thereof, in association with a pharmaceutically acceptable carrier or diluent.

The compounds of formula (I) and salts thereof may be formulated in a manner appropriate to the treatment for which it is to be used by bringing it into association with  
25 a pharmaceutically acceptable carrier or diluent. Preferably the composition is in a form suitable for parenteral administration. The compound may be included in

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a dosage form suitable for bolus injection or such as a tablet or capsule, for example a capsule comprising known formulation components. The compound may also be formulated for intravenous administration e.g. in a saline  
5 drip solution.

Suitable carrier or diluent materials for inclusion in the compositions of the present invention include organic or inorganic inert carrier or diluent material for example, water, gelatin, lactose, starch, magnesium  
10 stearate, talc, vegetable oils, gum arabic, polyalkylene-glycols, petroleum jelly and the like. The pharmaceutical compositions may be sterilised, pyrogen-free and isotonic. The compositions may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for  
15 varying the osmotic pressure or buffers. The pharmaceutical compositions may contain other therapeutically valuable substances.

The present invention further provides compounds of formula (I), as hereinbefore defined, and pharmaceutically  
20 acceptable salts thereof with the exclusion of (a) the compounds of formula (I) where  $R^1$  is hydrogen,  $X$  is  $-N=$ ,  $X^1$  is hydrogen and  $R^2$  is unsubstituted phenyl or 3-pyridyl, and  $R^1$  is hydrogen,  $X$  is  $-CH=$ ,  $X^1$  is hydrogen and  $R^2$  is 4-fluorophenyl, 3,4-dimethoxyphenyl, 3,4-ethylenedioxy or  
25 3,4,5-trimethoxyphenyl (but including 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo [1,2a] quinoxaline 5-oxide) for use in the treatment of the human or animal body

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in a method of therapy, for example treatment of a hypoxic tumour.

The invention further provides use of the compounds of formula (I) and pharmaceutically acceptable salts thereof (including compounds excluded by (a) and (b), from the compounds of the invention) in the manufacture of a medicament for use in the treatment of a tumour, for example a hypoxic tumour.

The following Examples illustrate the invention.

**EXAMPLE 1**

**1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide.**

Under an argon atmosphere, 1,2-dihydro-8-fluoro-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (4.0g, 14.2 mmol) and piperazine (12.2g, 0.142 mmol) were heated at 90°C in 2-propanol (20 ml) for 3.5h. The solvent was removed under reduced pressure and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 ml), washed with H<sub>2</sub>O (50 ml) and dried (MgSO<sub>4</sub>) and concentrated. The resulting orange solid was recrystallised from EtOAc/CH<sub>2</sub>Cl<sub>2</sub> to yield 4.2g (72%) of 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide, mp-212-214°C (Found : C; 68.2, H; 6.0, N; 19.6%, C<sub>20</sub>H<sub>21</sub>N<sub>5</sub>O.0.33H<sub>2</sub>O requires C; 68.0, H; 6.1, N; 19.8%).

1,2-Dihydro-8-fluoro-4-phenylimidazo[1,2-a]quinoxaline 5-oxide may be prepared as disclosed in EP-A-214632.

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**EXAMPLE 2**

**1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide.**

1,2-Dihydro-8-chloro-4-phenylimidazo[1,2-a] pyrido  
5 [3,2-e] pyrazine 5-oxide (0.1g, 0.335 mmol) and piperazine  
(0.288g, 3.35 mmol) were heated at 60°C in 2-propanol for  
0.5h under an argon atmosphere. The solution was cooled,  
evaporated and redissolved in 50ml CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O  
(50 ml), dried and evaporated to afford, after  
10 recrystallisation from EtOAc/CHCl<sub>3</sub>, 1,2-dihydro-8-  
(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e]  
pyrazine 5-oxide (72%) as an orange solid, mp=177-178°C  
(Found : C; 64.7, H; 5.7, N; 23.8%, C<sub>19</sub>N<sub>20</sub>N<sub>6</sub>O.0.33H<sub>2</sub>O requires  
C; 64.4, H; 5.8, N; 23.7%)

15 The product was converted to a bis-hydrochloride by  
reaction with 2.2 equivalents of HCl, using the procedure  
described in Example 4, (m.p.: greater than 250°C).

1,2-Dihydro-8-chloro-4-phenylimidazo[1,2-a] pyrido  
[3,2-e] pyrazine 5-oxide may be prepared as disclosed in  
20 EP-A-214632.

**EXAMPLE 3**

**1,2-Dihydro-4-(4-fluorophenyl)imidazo[1,2-a] pyrido [3,2-e]  
pyrazine 5-oxide.**

25 A mixture of 2-chloro-3-nitropyridine (0.44g, 2.8  
mmol) and 2-(4-fluorobenzyl)-2-imidazoline (0.5g, 2.79  
mmol) in CH<sub>3</sub>CN (8 ml) was heated at 80°C for 12 h in a

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nitrogen atmosphere. The solution was then left at room temperature overnight, evaporated and the residue purified on silica (MeOH/EtOAc, 1:10) to give 0.38g (48%) of 1,2-dihydro-4-(4-fluorophenyl)imidazo[1,2-a]pyrido [3,2-e] pyrazine 5-oxide after recrystallisation from MeOH, mp=213-215°C, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 4.1 (s, 4H), 6.8 (dd, 1H, J=8 and 8Hz), 7.0 (d, 2H, J=9.6Hz), 7.9 (d, 2H, J=9.6Hz) and 8.2 (m, 2H) ppm.

#### EXAMPLE 4

10 1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide bishydrochloride

8-Chloro-1,2-dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (1.0g, 3.36 mmol) and N,N,N'-trimethylethylenediamine (3.4g, 33.6 mmol) were heated at 90°C in 2-propanol (5 ml) for 3.5h. The solution was then evaporated and the residue purified on silica (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:10) to afford an orange foam (65%), of which 437 mg (1.0 mmol) was redissolved in 4 ml EtOAc/CH<sub>2</sub>Cl<sub>2</sub> (1:1), and 2.2ml of a 1.0M solution of HCl in Et<sub>2</sub>O, filtered and washed again with cold Et<sub>2</sub>O to give 1,2-dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide bishydrochloride mp=205-208°C (dec.) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 2.3 (s, 6H) 2.5 (t, 2H, J=7.2Hz), 3.1 (s, 3H), 3.75 (t, 2H, J=7.2Hz), 4.1 (s, 4H), 6.1 (d, 1H, J=8.4 Hz), 7.4 (m, 3H), 7.8 (m, 2H) and 8.05 (d, 1H, J=8.4Hz) ppm. (Found : C; 49.7, H; 6.4, N; 17.0%,

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$C_{20}H_{24}N_6O \cdot 2HCl \cdot 2.5H_2O$  requires C; 49.8, H; 6.3, N; 17.4%)

**EXAMPLE 5**

1,2-Dihydro-8-(1-methyl-1-hydroxyethylamino)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide hydrochloride

This compound was prepared in accordance with the procedure of Example 4 using 2-(methylamino)ethanol as nucleophile and with a reaction time of 1.5h and converted to a hydrochloride to afford 1,2-dihydro-8-(1-methyl-1-hydroxyethylamino)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide hydrochloride (63%) as a yellow solid, mp=228-230°C (dec.) (Found : C; 57.8, H; 5.3, N; 18.9%,  $C_{18}H_{19}N_5O_2 \cdot HCl$  requires C; 57.8, H; 5.3, N; 18.7%).

15

**EXAMPLE 6**

1,2-Dihydro-8-(1-aminopropyl)amino-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the procedure of Example 4 above using 1,3-diaminopropane as nucleophile and a reaction time of 1.5h. The residue after evaporation was triturated with EtOAc and the solid filtered and recrystallised from EtOAc to afford 1,2-dihydro-8-(1-aminopropyl)amino-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (57%) as orange crystals, mp=179-180°C (Found : C; 62.4, H; 6.0, N; 24.4%,  $C_{18}H_{20}N_6O \cdot 0.5H_2O$  requires C; 62.6, H; 6.1, N; 24.4%).

25

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**EXAMPLE 7**

1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a]  
pyrido [3,2-e] pyrazine 5-oxide bishydrochloride

This compound was prepared in accordance with the  
5 procedure of Example 4 above at 80°C for 2.5h using  
morpholine as the nucleophile, and the orange crystals  
which appeared upon cooling were filtered, washed with EtOH  
and recrystallised from 2-propanol, and converted to the  
hydrochloride using the procedure described above to yield  
10 1,2-dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a]  
pyrido [3,2-e] pyrazine 5-oxide bishydrochloride (74%),  
mp=224-226°C, (Found, C; 54.3, H; 5.3, N; 16.6%,  
C<sub>19</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>.2HCl requires C; 54.0, H; 5.0, N; 16.6%).

15 **EXAMPLE 8**

1,2-Dihydro-8-(4-cyclohexylpiperazin-1-yl)-4-phenylimidazo  
[1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the  
procedure of Example 4 above using 4-cyclohexylpiperazine  
20 as the nucleophile, and the orange crystals formed on  
cooling were collected and washed with 2-propanol. The  
product was recrystallised from 2-propanol to afford 1,2-  
dihydro-8-(4-cyclohexylpiperazin-1-yl)-4-phenylimidazo  
[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (78%), mp=188-  
25 189°C, (Found : C; 69.7, H; 7.0, N; 19.5%, C<sub>25</sub>H<sub>30</sub>N<sub>6</sub>O requires  
C; 69.8, H; 7.0, N; 19.5%).

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EXAMPLE 9

1,2-Dihydro-8-(2-methylaziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

8-Chloro-1,2-dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (0.25g, 0.84 mmol) was dissolved in 1.5 ml benzene and 0.3 ml Et<sub>3</sub>N, and 2-methylaziridine (0.2g, 3.5 mmol) were added and the solution stirred at 70-80°C for 1.5h. The solution was cooled and evaporated and the residue purified on silica (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:10) to afford 1,2-dihydro-8-(2-methylaziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (42%) as an orange waxy solid. The compound was analysed as the ring-opened hydrobromide, prepared by treating with 48% HBr in Me<sub>2</sub>CO, filtering and washing with cold Me<sub>2</sub>CO to give the ring-opened monohydrobromide, mp=200-201°C (dec.), (Found : C; 45.2, H; 4.1, N; 14.6%, C<sub>18</sub>H<sub>18</sub>N<sub>5</sub>OBr.HBr requires C; 44.9, H; 4.0, N; 14.6%).

EXAMPLE 10

1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the reaction conditions described for Example 4, using piperidine as nucleophile and at a reaction temperature of 60°C for 0.5h. Recrystallisation from 2-propanol afforded 1,2-dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (68%) as an orange solid,



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mp=185-187°C (Found : C; 69.1, H; 6.1, N; 20.2%,  $C_{20}H_{21}N_5O$  requires C; 69.2, H; 6.1, N; 20.2%).

**EXAMPLE 11**

5 1,2-Dihydro-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the procedure of Example 4, using N-(2,2,2-trifluoroethyl)piperazine as nucleophile to afford 1,2-dihydro-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (68%) as an orange solid after recrystallisation from ethanol, mp=221-222°C (Found : C; 58.7, H; 4.9, N; 19.6%,  $C_{21}H_{21}N_6OF_3$  required C; 58.6, H; 4.9, N; 19.5%).

15

**EXAMPLE 12**

1,2-Dihydro-8-(4-(2-pyridyl)piperazine-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the procedure of Example 4, except that the cooled reaction mixture was left at -18°C for 1h, and the orange crystals filtered and washed with 2-propanol to yield, after recrystallisation from 2-propanol, 1,2-dihydro-8-(4-(2-pyridyl)piperazine-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (55%), mp=201.5-202.5°C,  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  3.8 (m, 8H), 4.2 (s, 4H), 6.3 (d, 1H, J=8.4Hz), 6.75 (m, 2H), 7.4 (m, 3H), 7.8 (m, 3H), 8.3 (m, 1H), 8.35

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(d, 1H, J=8.4Hz) ppm.

The product was converted to a bishydrochloride as described for Example 4, mp=232-235°C (dec.)

5 EXAMPLE 13

1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a]  
quinoxaline 5-oxide

1,2-Dihydro-8-fluoro-4-phenylimidazo [1,2-a]  
quinoxaline 5-oxide (0.5g, 1.54 mmol) in 5 ml 2-propanol,  
10 was heated at 100°C for 8h with morpholine (1.5 ml, ca. 16.8  
mmol). The solution was then cooled and evaporated, and  
the residue purified on silica gel, eluting with EtOAc/MeOH  
(5:1), to yield 1,2-dihydro-8-(morpholin-1-yl)-4-  
phenylimidazo [1,2-a] quinoxaline 5-oxide (65%) as an  
15 orange solid, mp=232-233°C (dec.)

The product was converted to a monohydrochloride as described for Example 4 using 1.1 equivalents of HCl.

EXAMPLE 14

20 1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a]  
quinoxaline 5-oxide

This compound was prepared in accordance with the procedure of Example 13 to afford 1,2-dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (71%) as  
25 an orange solid, mp=230-231°C (dec.), monohydrochloride  
mp=246-247°C (dec.) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 1.8 (m, 6H), 3.4 (m, 4H),  
4.05 (s, 4H), 6.0 (d, 1H, J=2.4Hz), 6.5 (dd, 1H, J=2.4 and

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9.6Hz), 7.3 (m, 3H), 7.8 (m, 2H) and 8.0 (d, 1H, J=8.4Hz) ppm.

#### EXAMPLE 15

#### **1,2-Dihydro-8-(pyrrolidin-1-yl)-4-phenylimidazo [1,2-a] 5 quinoxaline 5-oxide**

This compound was prepared in accordance with the procedure of Example 13, to afford, as an orange solid, 1,2-dihydro-8-(pyrrolidin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide, mp=246-247°C (dec.), monohydrochloride  
10 mp>=275°C (dec.) <sup>1</sup>H-NMR δ 2.0 (m, 4H), 3.35 (m, 4H), 4.0 (s, 4H), 5.6 (d, 1H, J=2.4Hz), 6.2 (dd, 1H, J=2.4 and 9.6Hz), 7.3 (m, 3H), 7.75 (m, 2H) and 8.0 (d, 1H, J=8.4Hz) ppm.

#### EXAMPLE 16

#### **15 1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide bishydrochloride**

1,2-Dihydro-8-fluoro-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (0.5g, 1.7 mmol) and N,N,N'-  
trimethylethylenediamine (1.7g, ca.17 mmol) were heated at  
20 95°C for 24h, cooled and evaporated. The residue was purified on silica gel eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford an orange waxy solid (62%), which was converted into the bishydrochloride as described in Example 4 to give 1,2-dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-  
25 phenylimidazo [1,2-a] quinoxaline 5-oxide bishydrochloride, mp=> 250°C (dec.) <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.3 (s, 6H), 2.6 (t, 2H, J=7.2Hz), 3.05 (s, 3H), 3.5 (t, 2H, J=7.2Hz), 4.0

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(s,4H), 5.8 (d,1H,J=2.4Hz), 6.4 (dd,1H,J=2.4 and 9.6Hz),  
7.35 (m,3H), 7.7 (m,2H), and 8.0 (d,1H,J=8.4Hz) ppm.

**EXAMPLE 17**

5 **1,2-Dihydro-4-(3-pyridyl)-imidazo [1,2-a] pyrido [3,2-e]  
pyrazine 5-oxide**

2-Chloro-3-nitropyridine (0.22g, 1.4 mmol) and 2-(3-  
pyridyl)methyl-imidazoline (0.23g, 1.42 mmol) were heated  
at 85°C in acetonitrile for 4.5h. The solution was cooled,  
10 evaporated and the residue purified on silica, eluting with  
EtOAc/MeOH (10:1) to yield 1,2-dihydro-4-(3-pyridyl)-  
imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (50%) as  
deep yellow crystals after recrystallisation from EtOAc,  
mp=128-130°C, monohydrochloride mp=214-216°C (dec.) <sup>1</sup>H-NMR  
15 δ 3.6 (s,2H), 3.8 (s,2H), 6.7 (dd,1H,J=4.8 and 9.6Hz), 7.3  
(m,1H), 7.6 (m,1H) and 8.4 (m,4H) ppm.

**EXAMPLE 18**

**1,2-Dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine  
20 5-oxide hydrochloride**

This compound was prepared in accordance with the  
procedure of Example 17 using tolazoline in place of 2-(3-  
pyridyl)methyl-imidazoline and with a reaction time of 12h.  
Deep yellow crystals of the free base were obtained (63%)  
25 and recrystallised from MeOH, mp=194-195°C <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ  
3.6 (s,2H) 3.9 (s,2H), 6.6 (dd,1H,J=8 and 8Hz) and 8.3  
(m,2H) ppm. This material was converted into the

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monohydrochloride salt as described in Example 4, using 1.1 equivalents of HCl, to afford, as a yellow solid, 1,2-dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide hydrochloride, mp=238-240°C (dec.).

5

EXAMPLE 19

1,2-Dihydro-8-(aziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

8-Chloro-1,2-dihydro-4-phenylimidazo [1,2-a] pyrido  
10 [3,2-e] pyrazine 5-oxide (1.0g, 3.36 mmol) was stirred with aziridine 3.5g (81.4 mmol) at 25°C for 2h. The excess aziridine was evaporated at room temperature and the residue purified on silica eluting with ethyl acetate: triethylamine (99:1) to afford 1,2-dihydro-8-(aziridin-1-  
15 yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide as a deep yellow solid, recrystallised from ethyl acetate mp = 168-170°C, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.2 (s, 4H), 4.0 (bs, 4H), 6.4 (d, 1H, J=8.4Hz), 7.2 (m, 3H), 7.6 (m, 2H), and 8.0 (d, 1H, J=8.4Hz) ppm. (Found: C; 66.8, H; 4.6, N; 22.7%,  
20 C<sub>17</sub>H<sub>15</sub>N<sub>5</sub>O requires C; 66.9, H; 4.9, N; 22.9%).

EXAMPLE 20

1,2-Dihydro-8-methoxy-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

25 A solution of sodium methoxide in methanol (25%, 1mL) was stirred at room temperature together with 8-chloro-1,2-dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-

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oxide (0.1g, 0.34 mmol) for 2 hours. The solution was then heated for 1 hour at 80°C, cooled and water (1mL) added. The solution was evaporated, and redissolved in chloroform (25mL), then washed with water (25mL). The organic layer  
5 was dried and evaporated, and the residue purified on silica gel, eluting with ethyl acetate/hexane (1:1) to afford 1,2-dihydro-8-methoxy-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (75mg, 75%) as an orange solid which was recrystallised from mp 194-195°C. The product  
10 was converted to a monohydrochloride using the method described in Example 4, mp 223-224°C(dec.). Found: C; 64.8, H; 4.8, N; 19.2%,  $C_{16}H_{14}N_4O_2$  requires C; 65.3, H; 4.8, N; 19.0%.

**EXAMPLE 21**

15           1-2-Dihydro-8-(1-dimethylamino)ethoxy-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

8-Chloro-1,2-dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (1.0g, 3.4 mmol) was added slowly to a cooled solution of sodium N,N-dimethylethanolamine  
20 (6mL, 30% in N,N-dimethylethanolamine) and the solution stirred at room temperature for 12 hours, followed by 2 hours at 50°C. Water (50mL) was added and the solution extracted with ethyl acetate (3x100mL), dried and evaporated. The residue was purified on silica, eluting  
25 with ethyl acetate: methanol: ammonium hydroxide (47.5:47.5:5) to afford 1-2-dihydro-8-(1-dimethylamino)ethoxy-4-phenylimidazo [1,2-a] pyrido [3,2-e]

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pyrazine 5-oxide as an orange solid (0.7g, 69%)  
 recrystallised from ethyl acetate:methanol, mp 158-161°C,  
 (Found C; 61.0, H; 5.9, N; 18.8%,  $C_{19}H_{21}N_5O_2 \cdot 1.25 H_2O$  requires  
 C; 61.0, H; 6.3, N; 18.7%)

5 EXAMPLE 22

The toxicity of compounds prepared in the foregoing  
 Examples towards aerobic or hypoxic V79 Chinese hamster  
 cells in vitro is shown in Table 1. Toxicity was  
 determined by the use of the modified MTT assay (Stratford  
 10 and Stephens (1989), Int. J. Radiat. Oncol. Biol. Phys. 16  
 973-976). Values quoted represent concentration of drug  
 required to reduce proliferation of treated cultures by  
 50%. Cells are treated with various drug doses for 3 hours  
 at 37°C under aerobic or hypoxic conditions, following drug  
 15 removal cells are allowed to proliferate for 3 days prior  
 to assay.

TABLE 1

20	Compound	C air	C N <sub>2</sub>	Ratio
	mmol dm <sup>-3</sup>			
25	Example 1*	0.2	0.03	6.7
	Example 2	0.45	0.045	10
	Example 4	0.45	0.06	7.5
	Example 7	0.5	0.2	2.5
	Example 8	0.45	0.045	10
30	Example 12*	1.0	0.1	10
	Example 13	2.4	0.55	4.4
	Example 18	5.0	0.6	8.3
	Example 20	12.0	0.7	17.0
35	Example 21*	2.5	0.05	50

\* tested as free base.

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EXAMPLE 23

C3H mice in which the transplantable rodent tumour RIF-1 had been implanted subcutaneously were administered the compound of Example 2 (hydrochloride salt) [100 mg/kg] intraperitoneally immediately after irradiation with 25 Gy X-rays. The time for the tumour to increase in size to four times its original volume was 44 days compared with the corresponding time where no treatment was applied to the tumour (5 days) and where the tumour was treated by irradiation with 25 Gy X-rays alone (35 days).

The results show that the use of the compound immediately after irradiation to kill viable cells which were hypoxic at the time of irradiation, leads to a significant slowing in the growth of the tumour.

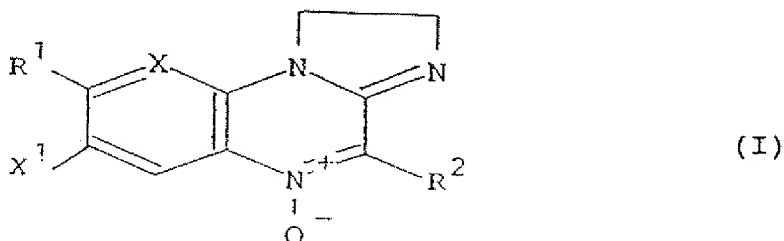


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CLAIMS

1. A quinoxaline or pyridopyrazine derivative of formula (I)

5



wherein R¹ is:

10 hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is

15 attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms

20 a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkoxy unsubstituted or substituted on

25 the amino group by one or two alkyl groups or by a divalent which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen

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substituents, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-alkyl)amino, or haloalkyloxy;

a heterocyclic group which is a 1-pyrrolidino, 1-  
5 piperidino, 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents, or an aziridino group unsubstituted or substituted by one or more or alkyl substituents; or

a 1-piperazino group which is unsubstituted or  
10 substituted by one or more alkyl, hydroxy or halogen substituents in the 2- or 3- position and in the 4-position is unsubstituted or N-substituted by haloalkyl, cycloalkyl of 5 to 7 carbon atoms (unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents), or pyridyl  
15 (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents) or phenyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents);

20  $R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen haloalkyl, alkyl, nitro, hydroxy alkoxy and alkylenedioxy;

X is -CH= or -N=; and

25  $X^1$  is hydrogen or halogen;

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms

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and the said haloalkyl groups contain one or more halogen atoms;

or a pharmaceutically acceptable salt thereof;

with the exclusion of (a) the compounds of formula

5 (I) where R<sup>1</sup> is hydrogen, X is -N=, X<sup>1</sup> is hydrogen and R<sup>2</sup> is unsubstituted phenyl or 3-pyridyl, and R<sup>1</sup> is hydrogen, X is -CH=, X<sup>1</sup> is hydrogen and R<sup>2</sup> is 4-fluorophenyl, 3,4-dimethoxyphenyl, 3,4-ethylenedioxy- or 3,4,5-trimethoxyphenyl and (b) the compound of formula (I) which  
10 is 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo [1,2a] quinoxaline 5-oxide.

2. A compound according to claim 1 wherein R<sup>1</sup> is:

hydrogen, alkyl, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the  
15 terminal amino group by one or two alkyl groups, aminoalkyl(N-alkyl)amino unsubstituted or substituted on the terminal amino group by one or two alkyl groups, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, haloalkylamino, haloalkyl(N-alkyl)amino;

20 a heterocyclic group which is a 1-pyrrolidino, 1-piperidino, 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents, or an aziridino group unsubstituted or substituted by one or more or alkyl substituents; or

25 a 1-piperazino group which is unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents in the 2- or 3- position and in the 4-position

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is unsubstituted or N-substituted by haloalkyl, cycloalkyl of 5 to 7 carbon atoms (unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents), or pyridyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents); and

$R^2$  is phenyl or pyridyl unsubstituted or substituted by one or more substituents selected from halogen haloalkyl, alkyl, nitro, hydroxy alkoxy and alkylenedioxy;

3. A compound according to claim 1 or 2 in which  $R^1$  is other than hydrogen.

4. A compound according to claim 1, 2 or 3 in which the group  $R^1$  is aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom, and optionally being substituted by one or more alkyl,

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hydroxyl or halogen substituents, aminoalkoxy unsubstituted or substituted on the amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-alkyl)amino, or haloalkyloxy.

5. A compound according to claim 4 in which R<sup>1</sup> is a group of formula (II)



wherein Y is -O- or -NR<sup>5</sup>-, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same or different and each is hydrogen or alkyl of 1 to 6 carbon atoms or form a heterocyclic ring containing from 5 to 7 carbon atoms, together with the amino nitrogen atom to which they are attached and optionally a further nitrogen or oxygen atom and a is 2 or 3;

or R<sup>1</sup> is a group of formula (III)



wherein Y<sup>1</sup> is -O- or -NR<sup>6</sup>-, R<sup>6</sup> is hydrogen or alkyl of 1 to 6 carbon atoms, Y<sup>2</sup> is halogen or hydroxyl, and b is 2 or 3.

6. A compound according to claim 1, 2 or 3 in which R<sup>1</sup> is unsubstituted or substituted 1-pyrrolidino, 1-

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piperidino, 1-morpholino or aziridino.

7. A compound according to claim 1, 2 or 3 in which R<sup>1</sup> is a 1-piperazino group N-substituted in the 4-position by haloalkyl, cycloalkyl, pyridyl or phenyl.

5 8. A compound according to any one of the preceding claims in which R<sup>2</sup> is substituted or unsubstituted phenyl.

9. A compound according to claim 8 in which R<sup>2</sup> is unsubstituted phenyl or 4-halophenyl.

10 10. A compound according to any one of the preceding claims in which X is -N=.

11. A compound according to any one of the preceding claims in which X<sup>1</sup> is hydrogen.

12. A compound according to claim 1 which is:

15

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide,

20

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-4-(4-fluorophenyl)imidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

25

1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a]pyrido [3,2-e] pyrazine 5-oxide,

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1,2-Dihydro-8-(1-methyl-1-hydroxyethylamino)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

5 1,2-Dihydro-8-(1-aminopropyl)amino-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

10

1,2-Dihydro-8-(4-cyclohexylpiperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

15 1,2-Dihydro-8-(2-methylaziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

20

1,2-Dihydro-8-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

25 1,2-Dihydro-8-(4-(2-pyridyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

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1,2-Dihydro-8-(morpholin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

5 1,2-Dihydro-8-(piperidin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

1,2-Dihydro-8-(pyrrolidin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

10 1,2-Dihydro-8-(1-methyl-1-(N,N-dimethylaminoethyl)amino)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

15 1,2-Dihydro-4-(3-pyridyl)-imidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

20 1,2-Dihydro-8-(aziridin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-methoxy-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide, or



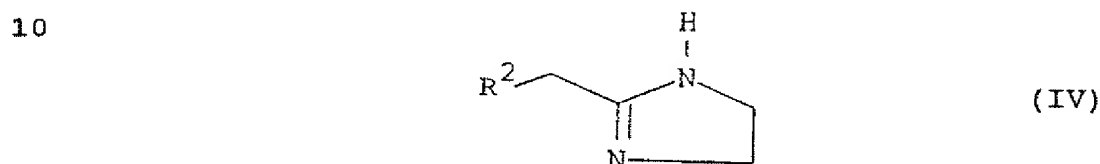
- 39 -

1,2-Dihydro-8-(1-(dimethylamino)ethoxy)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide;

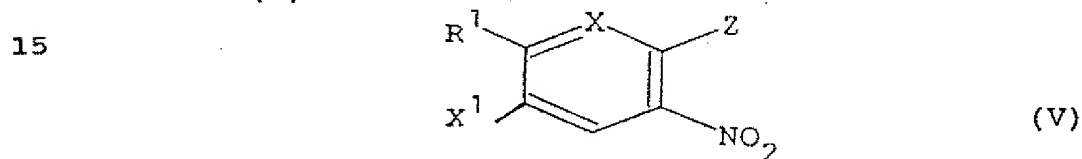
5 or a pharmaceutically acceptable salt thereof.

13. A process for producing a compound as claimed in any one of the preceding claims which comprises:

reacting a compound of formula (IV):-



wherein R² is as defined in claim 1, with a compound of formula (V):-



wherein Z is halogen, and R¹, X and X¹ are as defined in claim 1; or

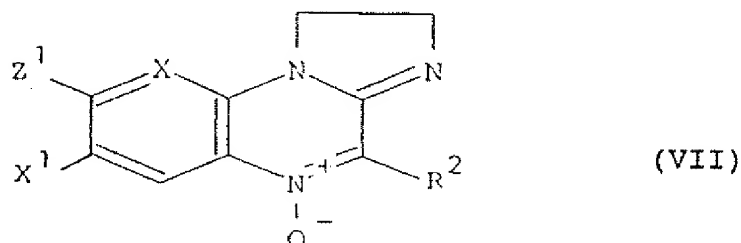
20 where R¹ is other than hydrogen, alkyl, alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy, reacting a compound of formula (VI):-



in which R¹ is as defined in claim 1 and is other than hydrogen, alkyl, unsubstituted or substituted aminoalkoxy,

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hydroxyalkoxy or haloalkoxy, with a compound of formula (VII):-



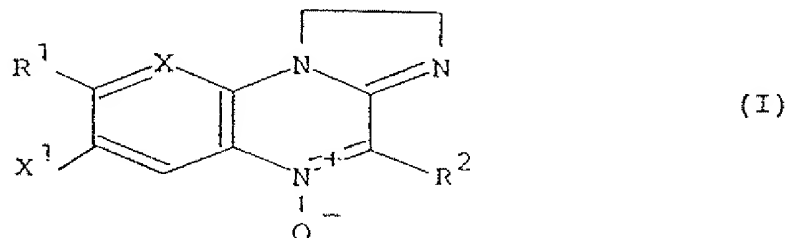
in which Z¹ is halogen and X, X¹ and R² are as defined in claim 1; or

where R¹ is alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy reacting a metal alkoxide (VIA)



in which R¹ is alkoxy, unsubstituted or substituted aminoalkoxy, hydroxyalkoxy or haloalkoxy, and M is a metal, with a compound of formula (VII) as hereinbefore defined; and optionally, converting the compound of formula (I) thus obtained to a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition which comprises a quinoxaline or pyridopyrazine derivative of formula (I)



wherein R¹ is

hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the

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terminal amino group by one or two alkyl groups or by a  
divalent group which forms a saturated heterocyclic ring  
together with the amino nitrogen atom to which it is  
attached optionally containing a further oxygen or nitrogen  
5 atom and optionally being substituted by one or more alkyl,  
hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino  
unsubstituted or substituted on the terminal amino group by  
one or two alkyl groups or by a divalent group which forms  
a saturated heterocyclic ring together with the amino  
10 nitrogen atom to which it is attached optionally containing  
a further oxygen or nitrogen atom and optionally being  
substituted by one or more alkyl, hydroxyl or halogen  
substituents, aminoalkoxy unsubstituted or substituted on  
the amino group by one or two alkyl groups or by a divalent  
15 which forms a saturated heterocyclic ring together with the  
amino nitrogen atom to which it is attached optionally  
containing a further oxygen or nitrogen atom and optionally  
being substituted by one or more alkyl, hydroxyl or halogen  
substituents, hydroxyalkylamino, hydroxyalkyl(N-  
20 alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-  
alkyl)amino, or haloalkyloxy;

a heterocyclic group which is a 1-pyrrolidino, 1-  
piperidino, 1-morpholino group, unsubstituted or  
substituted by one or more alkyl, hydroxy or halogen  
25 substituents, or an aziridino group unsubstituted or  
substituted by one or more or alkyl substituents; or  
a 1-piperazino group which is unsubstituted or

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substituted by one or more alkyl, hydroxy or halogen  
substituents in the 2- or 3- position and in the 4-position  
is unsubstituted or N-substituted by haloalkyl, cycloalkyl  
of 5 to 7 carbon atoms (unsubstituted or substituted by one  
5 or more alkyl, hydroxy or halogen substituents), or pyridyl  
(unsubstituted or substituted by one or more alkyl,  
haloalkyl, hydroxy, alkoxy, nitro or halogen substituents)  
or phenyl (unsubstituted or substituted by one or more  
alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen  
10 substituents);

$R^2$  is a hydrocarbyl or heterocyclyl aromatic group  
unsubstituted or substituted by one or more substituents  
selected from halogen haloalkyl, alkyl, nitro, hydroxy  
alkoxy and alkylenedioxy;

15 X is  $-CH=$  or  $-N=$ ; and

$X^1$  is hydrogen or halogen;

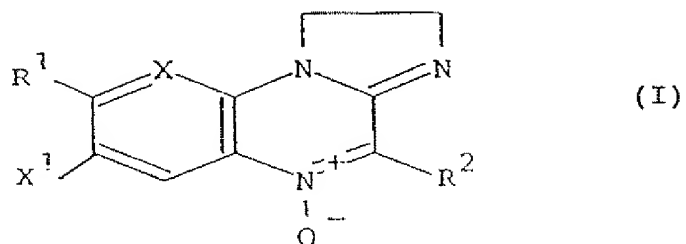
wherein the said alkyl groups and moieties  
incorporating alkyl groups contain from 1 to 6 carbon atoms  
and the said haloalkyl groups contain one or more halogen  
20 atoms;

or a pharmaceutically acceptable salt thereof;

in association with a pharmaceutically acceptable  
carrier or diluent.

15. A quinoxaline or pyridopyrazine derivative for  
25 use in the treatment of the human or animal body in a  
method of therapy, which is of formula (I)

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5 wherein R¹ is:

hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring

10 together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino unsubstituted or substituted on the terminal amino group by

15 one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen

20 substituents, aminoalkoxy unsubstituted or substituted on the amino group by one or two alkyl groups or by a divalent which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally

25 being substituted by one or more alkyl, hydroxyl or halogen substituents, hydroxyalkylamino, hydroxyalkyl(N-alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-

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alkyl)amino, or haloalkyloxy;

a heterocyclic group which is a 1-pyrrolidino, 1-piperidino, 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents, or an aziridino group unsubstituted or substituted by one or more or alkyl substituents; or

a 1-piperazino group which is unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents in the 2- or 3- position and in the 4-position is unsubstituted or N-substituted by haloalkyl, cycloalkyl of 5 to 7 carbon atoms (unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents), or pyridyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents) or phenyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents);

$R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen haloalkyl, alkyl, nitro, hydroxy alkoxy and alkylenedioxy;

X is  $-CH=$  or  $-N=$ ; and

$X^1$  is hydrogen or halogen;

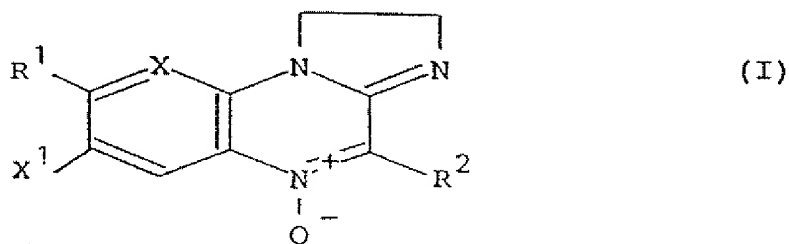
wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms and the said haloalkyl groups contain one or more halogen atoms;

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or a pharmaceutically acceptable salt thereof;

with the exclusion of (a) the compounds of formula (I) where R<sup>1</sup> is hydrogen, X is -N=, X<sup>1</sup> is hydrogen and R<sup>2</sup> is unsubstituted phenyl or 3-pyridyl, and R<sup>1</sup> is hydrogen, X is  
 5 -CH=, X<sup>1</sup> is hydrogen and R<sup>2</sup> is 4-fluorophenyl, 3,4-dimethoxyphenyl, 3,4-ethylenedioxy- or 3,4,5-trimethoxyphenyl.

16. Use in the manufacture of a medicament for use in the treatment of a tumour of a quinoxaline or pyrido-  
 10 pyrazine derivative of formula (I)



15 wherein R<sup>1</sup> is:

hydrogen, alkyl, alkoxy, alkylamino, dialkylamino, aminoalkylamino unsubstituted or substituted on the terminal amino group by one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring  
 20 together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkyl(N-alkyl)amino unsubstituted or substituted on the terminal amino group by  
 25 one or two alkyl groups or by a divalent group which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing

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a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, aminoalkoxy unsubstituted or substituted on the amino group by one or two alkyl groups or by a divalent  
5 which forms a saturated heterocyclic ring together with the amino nitrogen atom to which it is attached optionally containing a further oxygen or nitrogen atom and optionally being substituted by one or more alkyl, hydroxyl or halogen substituents, hydroxyalkylamino, hydroxyalkyl(N-  
10 alkyl)amino, hydroxyalkyloxy, haloalkylamino, haloalkyl(N-alkyl)amino, or haloalkyloxy;

a heterocyclic group which is a 1-pyrrolidino, 1-piperadino, 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen  
15 substituents, or an aziridino group unsubstituted or substituted by one or more or alkyl substituents; or

a 1-piperazino group which is unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents in the 2- or 3- position and in the 4-position  
20 is unsubstituted or N-substituted by haloalkyl, cycloalkyl of 5 to 7 carbon atoms (unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents), or pyridyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents)  
25 or phenyl (unsubstituted or substituted by one or more alkyl, haloalkyl, hydroxy, alkoxy, nitro or halogen substituents);



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$R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy;

5       X is  $-CH=$  or  $-N=$ ; and

$X^1$  is hydrogen or halogen;

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms and the said haloalkyl groups contain one or more halogen  
10 atoms;

or a pharmaceutically acceptable salt thereof.

$R^2$  is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen haloalkyl, alkyl, nitro, hydroxy,  
15 alkoxy and alkylenedioxy;

X is  $-CH=$  or  $-N=$ ; and

$X^1$  is hydrogen or halogen;

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms  
20 and the said haloalkyl groups contain one or more halogen atoms;

or a pharmaceutically acceptable salt thereof.

PCT/GB 93/01950

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D487/04 C07D471/14 A61K31/495 //(C07D487/04,  
241:00, 235:00) (C07D471/14, 241:00, 235:00,  
221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 214 632 (SEARLE) 18 March 1987 cited in the application see page 5, line 8 - page 6, line 6; claims 1,7; examples 5,8,11 --- -/--	1-3,7-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 December 1993

Date of mailing of the international search report

20. 12. 93

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax (+ 31-70) 340-3016

Authorized officer

Alfaro Faus, I

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 101, no. 7, 1984, Columbus, Ohio, US;  abstract no. 55037b,  P.C. PARTHASARATHY ET AL 'Heterocycle N-oxides: Part II. Syntheses of new ring systems N-oxides of dihydroimidazo- and pyrimido(2,1-h)pteridines and azadihydroimidazo and pyrimido(1,2-a)quinoxalines and their antiprotozoal activities.'  page 618 ;  see abstract and 11th collective index, page 34074, column 1, lines 78 - 85  &amp; INDIAN J. CHEM., SECT. B 1983, 22B(12),1233-5</p> <p style="text-align: center;">---</p>	8,14
X	<p>CHEMICAL ABSTRACTS, vol. 101, no. 7, 1984, Columbus, Ohio, US;  abstract no. 55038c,  P.C. PARTHASARATHY ET AL. 'Heterocyclic N-oxides: Part I. Syntheses of 1,2-dihydroimidazo(1,2-a)quinoxaline 5-oxides and 2,3-dihydro-1H-pyrimido(1,2-a)quinoxaline 6-oxides and their antiprotozoal activity'  page 618 ;  see abstract and 11th collective index, page 34098, column 2, lines 100,101 and column 3, lines 1-3,15-20,25-27  &amp; INDIAN J. CHEM., SECT. B 1983, 22B(12) 1250-1</p> <p style="text-align: center;">---</p>	14
P,X	<p style="text-align: center;">---</p> <p>WO,A,93 00900 (BRITISH TECHNOLOGY GROUP)  21 January 1993  cited in the application  see claims 1-18</p> <p style="text-align: center;">-----</p>	16

Information on patent family members

International Application No

PC/GB 93/01950

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP-A-0214632	18-03-87	US-A-	4696928	29-09-87
		AU-B-	587496	17-08-89
		AU-A-	6235786	12-03-87
		CA-A-	1282783	09-04-91
		DE-A-	3682244	05-12-91
		JP-A-	62063584	20-03-87
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WO-A-9300900	21-01-93	AU-A-	2197892	11-02-93
		GB-A-	2257361	13-01-93
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